Journal of Parkinson's Disease 4 (2014) 651–656
DOI 10.3233/JPD-140427
IOS Press

Research Report

Mild Cognitive Impairment and Parkinson's Disease - Something to Remember

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Abstract. Cognitive impairment is common in Parkinson's disease (PD), and many patients will eventually develop a dementia, which has a devastating impact on the patient and their family. As such, there has been much interest in identifying a prodromal state to inform prognosis and facilitate earlier management, similar to the concept of 'MCI' in the Alzheimer's field. However, grouping the early cognitive deficits of PD together as 'PD-MCI' may not be the best way forward as it implies a single aetiological basis with one clinical consequence. In this review, we argue that cognitive deficits in PD arise from a number of different pathological pathways, only some of which herald a dementing process. This has important implications both for treatment of individual patients, and for the design of future disease-modifying therapy trials.

Keywords: Parkinson's disease, mild cognitive impairment, dementia

INTRODUCTION

Parkinson's disease (PD), whilst classically a motor disorder, has long been recognised to have many non-motor features which map on to the pathology that is now known to extend outside of the dopaminergic cells of the substantia nigra and involve many different neuronal populations [1]. These non-motor features encompass a range of symptoms and signs, but perhaps the one most feared by patients and their families is the dementia of PD that can affect up to 50% of patients 10 years after diagnosis [2] and over 80% by 20 years [3]. As such many see the dementia of PD (PDD) as the inevitable consequence of having the disease for a long time, especially in the context of an aged CNS. If true then it must be possible to pick up the early features of this disease process ahead of the overt dementia, in much the same way as has been tried in Alzheimer's Disease (AD). In the Alzheimer's field, this prodromal state has been termed Mild Cognitive Impairment (MCI), often considered as an intermediate state between normal aging and dementia. However, whilst a useful concept, this is only a syndromic definition which does not necessarily imply a particular pathology. It is not always a reliable marker of incipient AD, with some patients never progressing or even improving [4]. As such the importance and value of this diagnostic entity has been questioned [5].

Nevertheless the principle of what MCI is trying to capture is a useful one, and the concept has of late been applied to PD, [6] even though concerns about doing this given the problems with its adoption in AD have been voiced [7]. Thus the question arises - can we use the term PD-MCI to capture a prodromal PDD state? This of course brings with it another question, what defines the MCI of PD and does it have a single aetiological basis and thus one clinical consequence? In this review we will argue that cognitive deficits in PD are common and arise from a number of different pathological pathways, only some of which herald a dementing process.

WHAT ARE THE COGNITIVE DEFICITS OF PD?

There is a long history of studies looking at the cognitive deficits of PD which have largely revolved around executive deficits that link to frontostriatal

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ISSN 1877-7171/15/$35.00

pathways, given that the core pathology in PD targets the basal ganglia circuitry [8]. These deficits include problems with planning and working memory-namely the capacity to store information online to solve ongoing cognitive problems. These deficits have been shown to occur at different stages of disease and to respond positively or negatively to dopaminergic therapies, [9] which has made the literature in this area complicated. However, the basis of these deficits seems to lie in dysfunctional dopaminergic networks which vary as a function of disease stage, drug therapy and the genotypic makeup of the patient (see below).

Another common cognitive deficit in PD is memory impairment, including problems with free recall [10] and learning new information [11]. These deficits can be hard to disentangle as in some instances the problem may relate more to issues of attention and impairment of executive search and retrieval strategies than to memory impairment per se, [12] whilst in others the memory deficits may relate to concurrent Alzheimer's-type pathology, which may occur in up to 50% of patients with PD dementia [13].

Finally visuospatial deficits can occur, [14] and indeed can dominate the cognitive problems in patients with Dementia with Lewy bodies (DLB) and PDD. These deficits are measurable in tasks involving copying complex figures and visual orientation and are likely to contribute to the occurrence of visual hallucinations and misrepresentations [15]. These problems probably reflect cortical Lewy body pathology and cholinergic deficits [16] but may also be exacerbated by drug therapies and other problems such as infections and metabolic disturbances.

Thus patients with PD may present with no cognitive deficits, deficits in a single cognitive domain or deficits in multiple cognitive domains. This nomenclature of single versus multi-domain MCI has been adopted by many to help describe the cognitive problem being reported [6, 17]. However we would posit that the domain affected may be more informative in terms of predicting progression than the number of domains affected.

WHAT CAN CAUSE THE COGNITIVE DEFICITS IN PD?

Patients with PD may do badly on tests of cognition for the following reasons:

- the intrinsic pathology of Parkinson's disease – namely the Lewy body pathology and cholinergic deficits;
- non PD pathology such as coexistent AD;
- drug therapies being taken for their PD and/or other conditions;
- depression or a major affective disorder;
- an acute confusional state secondary to another cause such as infection or metabolic disturbance;
- fatigue and somnolence making it hard for them to engage with cognitive tasks;
- low baseline cognitive function due to low educational attainment.

The recently proposed MDS PD-MCI criteria [6] attempt to exclude poor cognitive performance due to co-morbid conditions or severe affective or psychiatric disturbance, but nonetheless it is clear that cognitive deficits in PD often have a complex multifactorial basis. In addition it is debatable what actually constitutes a cognitive deficit- Is it when the patient performs, 1 or 1.5 or 2 standard deviations below their age/sex matched controls? Is it when they have a cognitive impairment that begins to impact on their function and activities of daily living?

Therefore it is not straightforward to say whether a patient actually has a cognitive deficit nor what this is due to. Longitudinal studies are crucial in terms of better describing these deficits and their significance for long-term prognosis. However, historically such studies have failed to give a consistent picture, implicating a number of different neuropsychological deficits as predictors of dementia in PD, including executive deficits, [18–20] poor verbal fluency, [20, 21] visuospatial dysfunction, [20] and language and memory deficits [19, 22]. This inconsistency is likely to relate to important methodological differences between these studies including the nature of the cohorts (hospital versus community-based), disease stage of patients included, and the choice of neuropsychological assessments. In our own CamPaIGN study, we attempted to overcome some of these problems with previous studies, by describing the evolution of cognitive problems from the time of diagnosis in a community-based cohort which was generalizable to the PD population as a whole.

Our original CamPaIGN study set about collecting all incident cases of PD over a 2 year period (December 2000–2002) in the county of Cambridgeshire in the UK using UKPDS Brain Bank criteria for diagnosis [23]. The cohort was a population-representative sample collected from the community and then followed up over time, with ongoing assessments until the present day. The patients could not have a dementia on entering the study (otherwise they would have

been defined as having DLB). They were examined with a detailed neuropsychological battery as well as a range of other standardised motor, affective and functional assessments. These assessments have been done every 2 years and the natural history of disease plotted, including conversion to dementia. In addition genotyping studies have been done on these patients to try and identify genetic factors that link to their cognitive course [2]. Using this approach we have described 2 cognitive syndromes in PD (see Fig. 1): [24]

(i) A frontostriatal executive syndrome that relates to changes in the dopaminergic networks and which varies as a function of disease stage, dopaminergic medication and COMT genotype. The deficits so identified can best be modelled using an inverted U-shaped relationship in which working memory or similar cognitive function has an optimal dopamine level. Too much or too little causes impairments in task performance. As such these deficits have a complex relationship to PD, but a simple one to PDD in that they are not predictive or associated with its development.
(ii) In contrast, the second type of cognitive syndrome does evolve into dementia, and is characterised in its early stages by visuospatial deficits (such as difficulty copying the interlocking pentagons found in the MMSE) as well as temporal lobe-based deficits (such as poor semantic, but not phonemic, fluency). These patients tend to be older at presentation and are more likely to possess the MAPT (tau) H1/H1 genotype and/or a heterozygote GBA mutation [25]. The underlying aetiology of this syndrome is likely to involve Lewy body pathology in posterior cortical regions, as well as cholinergic deficits in these areas [26].

Although as yet, not all aspects of this work have been fully replicated, there is nonetheless an emerging consensus from clinical [27, 28] and genetic studies [29] that the basic principles are true. Furthermore, studies using a range of imaging modalities including structural MRI [30], SPECT [31] and FDG-PET [32] to investigate PD patients with cognitive impairment support the hypothesis that pathological changes in posterior cortical regions are associated with progression to dementia in PD.

The existence of these two distinct syndromes may help us better understand the heterogeneity of cognitive deficits in PD and their prognostic relevance. However whilst helpful, this is not the whole story as some cognitive aspects of PD have alternate aetiologies such as problems with impulsivity and compulsivity which involve noradrenergic [33] and serotoninergic dysfunction [34] as well as dopaminergic dysfunction. In addition the amnesic deficits are hard to tie down in terms of specific network problems, and are unlikely to be due solely to AD pathology, although this may account for memory deficits in some PD patients, [13] particularly given that the average age of PD diagnosis is around 70 years in population-based cohorts [2]. In keeping with this, a decrease in amyloid-beta 1-42 in CSF, which is well demonstrated in Alzheimer's disease, has also been shown to predict more rapid cognitive decline in PD [35, 36]. Nevertheless the important point is that the MCI covers a range of deficits, with a variety of aetiologies and varying prognostic significance, and this in turn has important therapeutic implications.

HOW CAN WE TREAT THE COGNITIVE DEFICITS OF PD?

The above discussion enables one to predict how to approach the treatment of the cognitive deficits of PD, although therapeutic options at present are very limited. Typical strategies may include:

- manipulation of the dopaminergic agents being used for the motor aspects of the disorder, which may be contributing to executive dysfunction, and exacerbating hallucinations in the later stages of the disease;
- the use of cholinergic agents to boost the failing cholinergic system which is likely to be contributing to the 'posterior cortical' dementing syndrome;
- the treatment of any other disease feature that could be contributing to poor cognitive performance such as fatigue, somnolence or depression.

In all patients with cognitive impairment, a standard approach involves first looking at the drugs and or any other co-existent illnesses that may be driving it – e.g. a urinary tract infection or metabolic disturbance. In many cases the dopaminergic drugs are contributory: in the case of executive deficits they may be contributing to a hyperdopaminergic state which is detrimental to executive performance, [37] whilst in the more posterior cortical presentation of incipient PD dementia they may be aggravating the visual hallucinations and behavioural problems through stimulation of the dopaminergic network at this site. In view of this, dopaminergic drugs are often manipulated,

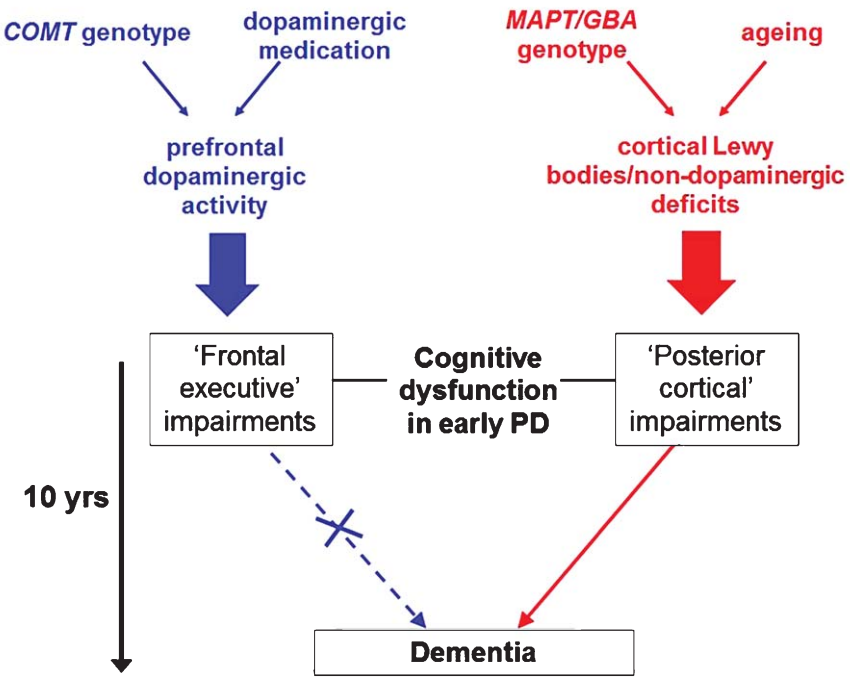

Fig. 1. Schematic representation of 2 distinct cognitive syndromes in early PD, which differ in terms of their underlying aetiological basis, and prognosis. (Adapted from Williams-Gray et al., [24]).

removing dopamine agonists and reducing the dose of L-dopa, although with this comes a worsening of their motor state. As such other agents are needed such as cholinesterase inhibitors for patients with incipient or early PDD [38]. Memantine, an NMDA receptor antagonist, has also shown some early promise in small randomised controlled trials in PDD [39]. In the case of the patients with more prominent executive deficits, there has been interest in agents that may have an alerting capacity such as modafanil, [40] as well as drugs targeting the noradrenergic system such as atomoxetine [33]. Another therapeutic strategy which is gaining an evidence base for early cognitive deficits in PD is cognitive training, [41, 42] although it remains to be seen whether demonstrated improvements on neuropsychological tests translate into real-world improvements in cognitive function.

Finally the significance of these cognitive syndromes is not restricted to their symptomatic treatment but may also facilitate more successful disease-modifying therapy trials. For example, our work indicates that newly-diagnosed PD patients with the H1/H1 MAPT genotype who are unable to accurately copy interlocking pentagons and cannot generate a list of at least 20 animals in 90 seconds in a semantic fluency task are at much higher risk of developing dementia within the next 5 years (PPV 58%) than patients exhibiting none of these risk factors (PPV 0%) [2]. If you therefore enriched for individuals within the former group and gave them a disease-modifying therapy, one would have a very good chance of seeing a significant effect over 5 years of follow-up using dementia as the primary end-point. In reality, most studies recruit individuals in the latter group with no demonstrable cognitive impairment at baseline, and in this group, there is no chance of seeing any effect of treatment on dementia incidence, and measuring disease progression using standard motor measures is almost impossible given the confounding effects of symptomatic therapy. Thus better understanding early cognitive deficits of PD and their significance may have an important impact on the future of disease-modifying therapy trials.

CONCLUSION

In this review, we have highlighted the fact that cognitive impairments in PD are common, but these cognitive deficits represent a range of pathologies and each carries a different significance for patients, as well as therapeutically. Thus encompassing all these deficits

under a single 'PD-MCI' syndrome may not be appropriate. It is now critical for the field to better define the causes of the different types of cognitive deficits in PD, and how they relate to each other and to the development of dementia. By so doing, we will avoid some of the problems that have dogged the field of MCI in AD, as well as enabling more productive trials of disease modifying therapies that could ultimately slow down the development of the most feared complication of PD, namely the dementia associated with it.

ACKNOWLEDGMENTS

We would like to thank all those that have funded our work over the years including the Wellcome Trust, MRC, Patrick Berthoud Trust, Parkinson's UK, the Van Geest Foundation and the NIHR award of a Biomedical Research Centre to the University of Cambridge and Addenbrooke's NHS trust. We would also like to thank all the patients who have so willingly signed up to be involved with our research.

CONFLICT OF INTEREST

We have no conflict of interest to report.

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